Update on the Current Mercury RfD & the Implications for Revisions Based on Recent Data

Alan H. Stern, Dr. P.H., DABT
Division of Science, Research and Technology
New Jersey Dept. Environmental Protection

Cardiovascular Endpoint

- Effects associated specifically with MeHg
  - some health effects currently associated only with inorganic Hg
    - e.g., cardiomyopathy
  - not known to what extent inorg. and MeHg share common mode of action for cardiovascular effects

- **Heart Disease**
  - including AMI, MI, CHD, ischemic heart disease
  - Salonen et al. (1995)
    - Finland – 1833 middle-aged men in health registry
    - mean fish intake = 46.5 g/day
      - **90th percentile of U.S. consumers**
    - mean Hg hair = 1.92 ppm
      - **~ 90th percentile of U.S. males**
    - hair Hg = 2 ppm, or $30 g fish/day
      - **RR = 1.7 for AMI, (p = 0.038)**
    - **Hair Hg assoc. with immune complexes with oxidized LDL**

- Follow up of Finnish cohort additional 4 years (Rissanen, 2000)
  - prospective measurement of fish n-3 fatty acids
    - **upper quintile of n-3 fatty acids AND hair Hg < 2 ppm → 52% reduction in risk**
    - **upper quintile n-3 fatty acids AND Hg > 2 ppm → 24% reduction in risk**
      - **Hg > 2 ppm reduced protective effect of n-3's by ~ 50 %**
  - implies balance between protection of n-3's and adverse effects of MeHg

- Multi-center study (Europe and Israel) (Guallar et al. 2002)
  - men #70 yrs.
  - case control - first AMI
  - DHA (n-3 fatty acid)
  - toenail Hg
    - interpretation of exposure?
  - with full model adjustment, (including n-3's) OR for AMI in highest quintile Hg was 2.2 times OR in lowest quintile
    - monotonic positive dose-response
  - dose response modeling for DHA gave monotonic negative trend
  - Consistent with Hg antagonism of n-3 protection

- U.S. health care professionals study (Yoshizawa et al. (2002)
  - case-control study of coronary heart disease
    - middle-aged men
    - toenial Hg
      - Hg conc. larger than largest group in Guallar et al.
    - n-3 fatty acids
  - dentists were largest group
    - 63% of controls
    - Hg exposure > twice that of other groups
      - occupational exposure to Hg^0 ?

- toenail Hg not associated with risk of CHD
  - for total cases
  - with dentists excluded OR = 1.3-1.7
    - higher OR with adjustment for n-3's
    - not significant – small n
- does putative association result from total Hg or MeHg?
  - if MeHg, then inclusion of dentists is a confounder
- potential exposure misclassification
  - toenail samples collected up to 5 yrs. prior to CHD event

- Minamata
  - preliminary ecological study comparing causes of death in two heavily exposed districts of Minamata to Minamata City as a whole (Tamashiro et al., 1988)
  - diseases of the heart were not elevated
    - period of analysis was approx 20 years after initial disease report
    - peak period for heart disease my not have been included
    - MeHg exposure in control area not documented
  - case-control study in Kumamoto prefecture
    - causes of death secondary to Minamata disease analyzed

- OR not significant for any cause
  - ischemic heart disease - OR = 1.3 males 0.65 females
  - other heart disease - OR = 1.3 males 2.0 females
  - only ischemic heart disease sig. associated with Minamata disease on death certificates

- Atherosclerosis
  - Salonen et al. (2000) measured progression in men from E. Finland
    - ultrasound measurement of thickness of carotid artery
    - two measurements 4 yrs. apart
  - hair Hg
    - upper quintile = 2.81 ppm
  - multivariate regression model
    - Hg highly significant
    - beta for Hg second only to systolic BP
    - 7.3% increase in progressive thickening for each ppm Hg in hair

- **Blood pressure and heart rate – *in utero* exposure**
  - Some evidence for association of *in utero* MeHg exposure (cord blood Hg) and BP at 7 yrs. (Faroese cohort, Sørensen et al., 1999)
    - systolic and diastolic
    - dose response plateaus at low exposures (10 ug/l)
  - Also decrease in heart rate *variability*
- Inconsistent with findings in institutionalized patients with "fetal Minamata disease" (Oka et al., 2003)
- Animal studies examined adolescents and adults
  - some associations, but generally high dose effects with frank neurological toxicity

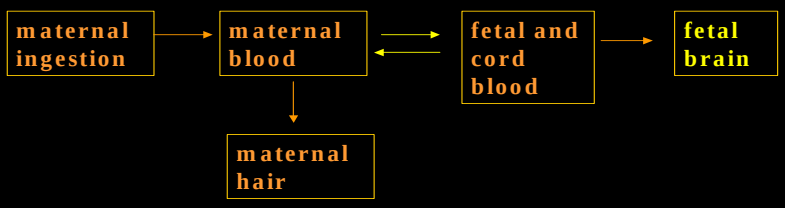
Summary of Cardiovascular Effects

- Epidemiological studies suggest an association between heart disease (including but not limited to AMI) and MeHg
- Causal mechanism suggested by apparent antagonism between n-3 fatty acids and MeHg
  - anti-oxidant properties of n-3's and lipid peroxidation stress from MeHg?
  - different levels of n-3's and MeHg by species may explain differences among studies of potential cardiovascular benefits of fish consumption
  - risks from MeHg may not be straightforward, but would be expected to be mediated by n-3 exposure

- association between atherosclerosis and MeHg seen only in single study
  - mechanism may be consistent with lipid peroxidation by MeHg
- Salonen et al., 1995, and Guallar et al. (2002) may lend themselves to dose-response modeling
  - lack of information about toenail Hg as a biomarker makes Guallar study less useful
- Evidence for effects of MeHg on BP at current levels of exposure is weaker
  - no epi. studies in adults
  - animal data difficult to interpret given multiple toxicities
  - *in utero* BP effects are unclear with respect to persistence and long-term implications
  - of concern

Reassessment of the pharmacokinetic model for dose reconstruction

Pharmacokinetic Pathway for Fetal Exposure to MeHg



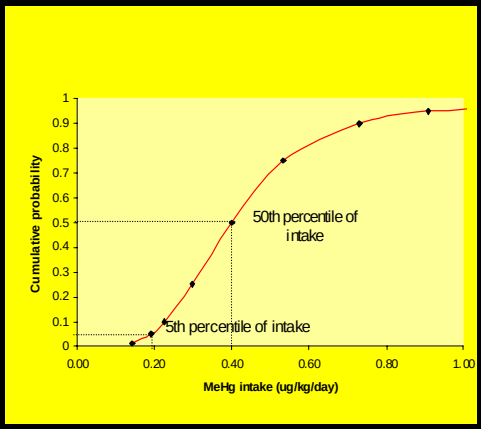
One Compartment Pharmacokinetic Model

(for blood)

$$D = \frac{Cc \times R \times b \times V)/(A \times F)}{W}$$

Pharmacokinetic Variability in Pathway

based on one-compartment model
(Stern, 1997)



- Previous analyses have produced consistent estimates of population variability in the dose reconstruction

Estimate of Pharmacokinetic Variability
Dose-Blood
from 3 studies

	50th percentile/ 5th percentile (95% of var.)	50th percentile/ 1st percentile (99% of var.)
Stern (1997)	mean = 1.8	mean = 2.4
Swartout and Rice (2000)	2.1	2.8
Clewell et al. (1999)	1.4	1.7

- However, previous analyses were inconsistent in absolute values predicted for the dose
  - this was largely a function of differences in central tendency estimates
  - selection of appropriate data sets and central tendency estimates was uncertain
  - analyses differed with respect to the specificity of the parameter values to pregnancy and stage of pregnancy
- Also, previous analysis implicitly assumed that $Hg_{cord}/Hg_{maternal} = 1.0$

- Current re-analysis is largely third-trimester-specific
  - reflecting pharmacokinetic factors which influence Hg conc. in cord blood
- Current re-analysis incorporates the

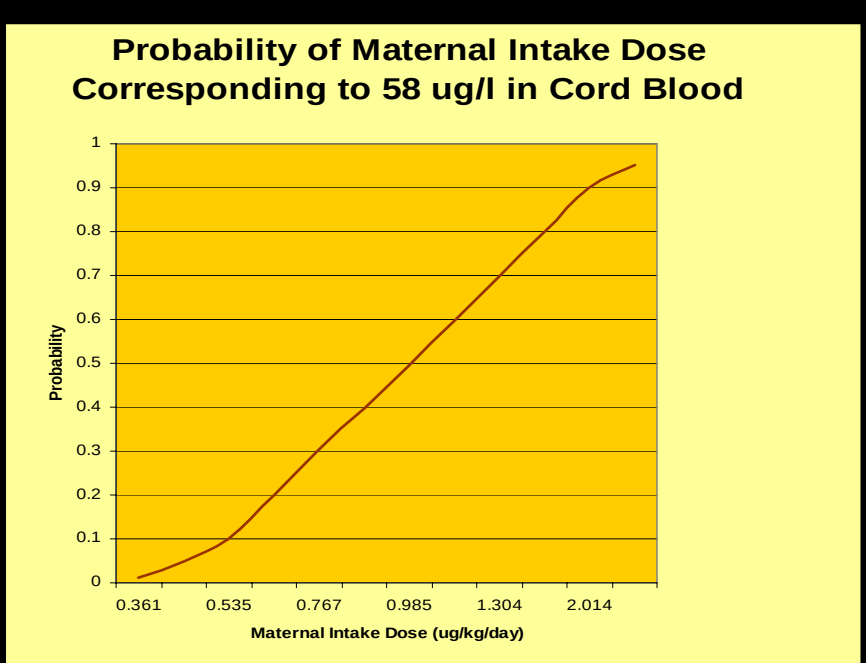
  $Hg_{cord}/Hg_{maternal}$ ratio

- W – data on maternal weight at delivery
  - correlated with V
- V - data on third-trimester total blood volume
- b – data on elimination rate (T ½) from pregnant women in Iraqi poisoning
- F – not pregnancy specific
  - however, may not significantly change during pregnancy
  - uncertain parameter
- A – not pregnancy specific
  - unlikely to vary much with pregnancy
- R – delivery-specific
  - well documented

Preliminary results of revised dose reconstruction

Maternal dose (ug/kg/day) corresponding to 58 ug/l in cord blood

		current EPA value
mean	1.03	1.08
s.d.	0.73	
1st percentile	0.21	
5th percentile	0.31	
10th percentile	0.39	
50th percentile	0.84	
50th percentile/5th percentile	2.7	
50th percentile/1st percentile	4.0	3 (assumed)



- Thus, on the basis of the preliminary analysis:
  - the estimate of the mean maternal dose is about the same as EPA's previous estimate
  - the overall variability in the dose reconstruction is approximately 33% larger than the EPA assumed value
    - appears to be due largely to the variability in the cord/maternal ratio

  - If a UF approach is used to address pharmacokinetic variability, the preliminary analysis suggests that a UF of approx. 4 may be justified
    - **99% of population variability**
  - However, the third-trimester specificity of the analysis suggests that 99th percentile estimate can be used directly in the RfD calculation
    - **58 ug/l . 0.21 ug/kg/day**
  - If a UF (toxicodynamic factors, database insufficiency etc.) of 3 is then applied, overall RfD could be
    - **0.21 ug/kg/day/3 = 0.07 ug/kg/day**